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(54) X-ray contrast agents

(57) The invention describes a new type of X-ray contrast agent. It has been found that iodinated alkenes with one or more C=C double bonds substituted with electronically neutral substituents and iodine can be used as X-ray contrast agents. Novel iodoalkene compounds are also described.

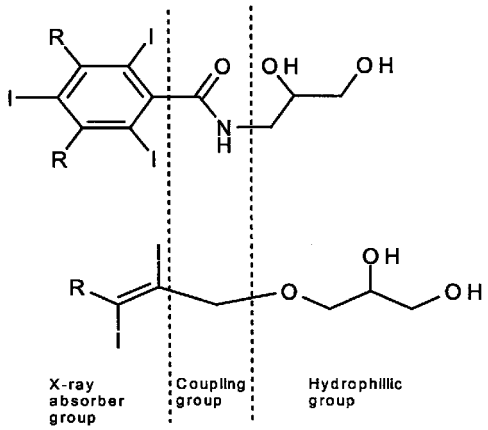

Figure 4: X-ray absorber group, coupling group and hydrophilic group in triiodobenzene- and iodoalkene-derivatives

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Description

[0001] This invention describes a new type of X-ray contrast agents including their formulation and use. It has been found that iodinated alkenes can be used as X-ray contrast agents like the traditional iodinated aromatic contrast agents. The invention covers new iodinated alkenes, their use as X-ray contrast agents, as well as the use of known iodoalkenes as X-ray contrast agents.

[0002] Many of today's X-ray contrast agents are based on triiodinated aromatics. The product iohexol (Omnipaque®) by Nycomed Imaging AS, given in figure 1, is an example of such a triiodinated aromatic.

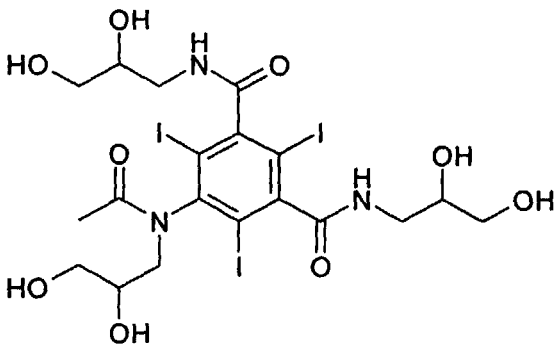


Figure 1: Iohexol

[0003] There is a continuing need for new X-ray contrast agents, especially compounds with simpler structures than the traditional iodinated aromatic compounds. Such compounds can be prepared with fewer and easier synthetic steps than necessary for the preparation of triiodinated aromatic X-ray contrast agents.

[0004] It has previously been investigated whether certain iodinated alkenes could be used as X-ray contrast agents. H. Suter & H. Zutter describe in Pharm. Acta Helv. *50*, 151-152, 1975, how fumaric acid derivatives were tested as potential X-ray contrast agents. Several fumaric acid derivatives were synthesised with different substituents that should give high aqueous solubility. One of those was diiodofumaric acid bis-[diethanolamide]. The toxicity (LD 50 in mice, intravenous) was found to be less than 1g/kg for all substances. The corresponding value for iohexol is 33.7 g/kg. The reason for this high toxicity is probably that the diiodofumaric acid structures are equivalent to a "vinylogeous acid-iodide" that can release iodide by an addition-elimination reaction with nucleophiles, see figure 2.

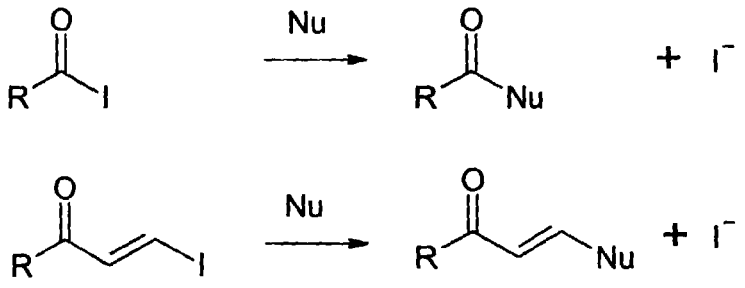


Figure 2: Iodide release from an iodoalkene with an electron withdrawing substituent, Nu = Nucleophile

[0005] Fumaric acid derivatives and other iodoalkenes with electron withdrawing substituents will probably be unsuitable as X-ray contrast agents. The reason is that such compounds are able to release toxic iodide by an addition-elimination reaction with nucleophiles. In the development of new X-ray contrast agents it is generally desired that the contrast agent affects the different biological mechanisms in the body as little as possible, because this generally results in lower toxicity and less negative clinical effects. Compounds that can release iodide in reactions with nucleophiles or

electrophiles may cause toxic and negative biological effects and should not be used as contrast agents.

[0006] Iodoalkenes with electron-donating substituents may add electrophiles in the same way as enamines, see figure 3. This is undesirable too since the ammonium group can be cleaved hydrolytically. In addition the iodine is now bound to an sp^3 hybridized carbon which is characteristic for alkylating agents. Again, attack of nucleophiles will release iodide.

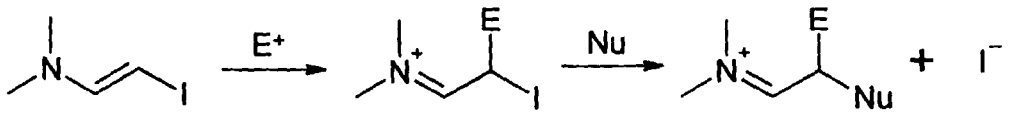


Figure 3: Iodide release from an iodoalkene with an electron donating substituent, E+ = Electrophile, Nu = Nucleophile

[0007] Partly as a result of the negative results from the investigation of fumaric acid derivatives, it has been generally accepted that only iodinated aromatic compounds can be used as X-ray contrast agents. Other types of highly-iodinated compounds that possess the properties required for X-ray contrast agents such as aqueous solubility, non-toxicity and stability have not yet been found.

[0008] It has now surprisingly been found that it is possible to use iodinated alkenes as X-ray contrast agents equivalent to iodinated aromatic contrast agents. The iodinated alkenes of the present invention differ from the compounds described by Suter and Zutter in that they contain neither electron-withdrawing nor electron-donating substituents at the C=C double bond. As a consequence there should be no problems caused by addition of electrophiles or nucleophiles followed by loss of iodide.

[0009] A comparison of the structures of a triiodobenzene derivative and an iodoalkene is given in figure 4. In figure 4 an X-ray absorber group, coupling group and hydrophilic group are distinguished. In order to indicate each group the molecules are divided by two dotted lines.

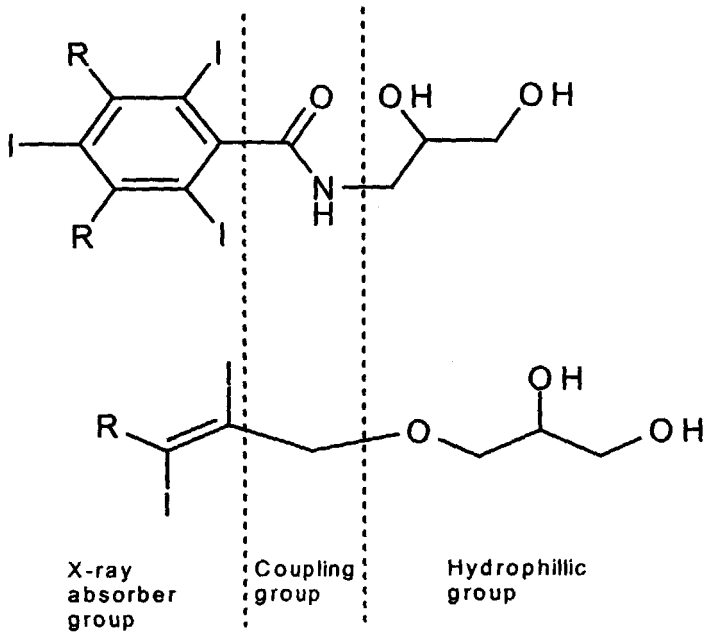
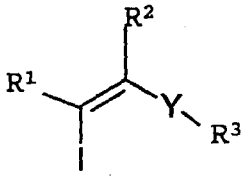


Figure 4: X-ray absorber group, coupling group and hydrophilic group in triiodobenzene- and iodoalkene-derivatives

[0010] Compared with triiodobenzene derivatives some of the iodoalkene compounds described in this invention introduce something new in all three subgroups. The iodoalkene compounds have an iodoalkene as the X-ray absorber group, methylene as coupling group and a hydrophilic group containing both ether and hydroxyl groups.

[0011] The present invention therefore addresses the use of iodoalkenes as X-ray contrast agents. X-ray contrast agents in accordance with the invention are characterised by electronically neutral substituents at the iodinated C=C double bond(s), meaning that the substituents do not have an electron-donating or electron-withdrawing effect. Electronically neutral substituents are called C-substituents or C-groups in contrast to electron donating X-substituents or electron withdrawing Z-substituents. (Ian Fleming: Grenzorbitale und Reaktionen organischer Verbindungen, p. 57, Verlag Chemie 1979). The donor/acceptor properties of substituents can be described by Hammett substituent constants σ_m or σ_p, resonance effect parameter R and field/inductive effect parameter F (C. Hansch, A. Leo and R. W. Taft, Chem. Rev. 1991, *91*, 165-195). The electron donor/acceptor effect of substituents acting through space is called a field effect, whereas the effect acting through σ-bonds is called an inductive effect. The electron donor/acceptor effect of substituents on double bonds or aromatic rings originating from the substituent's π- or non-bonding n-electrons is called a resonance effect.

[0012] In one aspect, the present invention provides X-ray contrast compositions (ie. both X-ray agents and X-ray contrast media) comprising compounds of formula A:



A

where

$Y = (IC{=}CI)_n$ where n is 0 or 1, and the groups R^1 and R^2 are iodine or Q, and R^3 is Q.
Q is a group that is electronically neutral, ie. a "C-substituent" or "C-group" which has neither an electron donating nor electron-withdrawing effect. It is preferred that the Q groups each independently have values for resonance effect R and field effect F in the range: $0.06 \geq R \geq -0.45$ and $0.24 \geq F \geq -0.03$.
More preferred are Q groups in the range $0.04 \geq R \geq -0.39$ and $0.22 \geq F \geq -0.02$.
Most preferred are Q groups in the range $0.02 \geq R \geq -0.33$ and $0.20 \geq F \geq -0.01$.

[0013] Figure 8 in appendix 1 shows a plot of the resonance effect parameter R and the field/inductive effect parameter F for different substituents. Strong field/inductive acceptors like NO_2 (F = 0.65) have high positive F-values. Strong resonance donors like NMe_2 (R = -0.98) have high negative R-values. The preferred electronically neutral substituents (Q) are located in the neighbourhood of CH_2OMe (F = 0.13 and R = -0.12).

[0014] R^1, R^2 and R^3 can further be the same or different.

[0015] It is further preferred that the compounds contain at least 2 iodine atoms. An increase of the number of iodine atoms will give increased contrast effect. The IC=CI group of the present invention may be of either *cis* or *trans* (ie. E or Z) configuration.

[0016] The Q groups are preferably also hydrophilic, ie. are groups that contribute to the aqueous solubility of the contrast agent. The aqueous solubility increases with increasing number of hydrophilic groups. Hydroxylated alkyl chains are examples of hydrophilic Q groups.

[0017] The number of iodine atoms and the number of hydrophilic groups must be balanced in order to obtain the desired contrast effect and sufficient aqueous solubility.

[0018] Preferred are compounds with formula A for use in X-ray contrast agent compositions, wherein:

R^1 = H, I, CH_2OH or R^3;
R^2 = H, I, CH_2OH or R^3;
R^3 = H, CH_2-R^4, CH_2-R^5, $CH(R^4)_2$, CHR^4R^5, $CR^4(R^5)_2$, R^5 or $(CH_2)_{1\text{-}3}$-CO-NR^5R^6;
R^4 = O-R^5, O-$(CH_2CH_2\text{-}O)_{1\text{-}7}$-$R^6$, NH-CO-$R^6$, NH-CO-O-$(CH_2CH_2\text{-}O)_{1\text{-}6}$-$R^6$, NH-CO-O-$R^6$, NH-CO-$NH_2$, O-CO-$R^6$, O-CO-O-$R^6$ or O-CO-NH-R^6;

R^5 = H, or a C_{1-8} alkyl chain which is unbranched or branched and which is substituted with one or more OH-groups.
R^6 = H, a C_{1-7} alkyl chain or R^5.

[0019] More preferred compounds of formula A have:

R^3 = H, CH_2-R^4, CH_2-R^5, $CH(R^4)_2$, CHR^4R^5 or R^5;
R^4 = O-R^5, O-$(CH_2CH_2$-O$)_{1-7}$-R^6, NH-CO-R^6, NH-CO-O- R^6, O-CO-R^6, or O-CO-NH-R^6;
R^5 = H or a C_{1-7} alkyl chain which is unbranched or branched and which is substituted with one or more OH-groups.
R^6 = H, a C_{1-6} alkyl chain or R^5.

[0020] Most preferred compounds of formula A have:

R^3 = CH_2-R^4 or CH_2-R^5;
R^4 = O-R^5, O-$(CH_2CH_2$-O$)_{1-6}$-R^6, O-CO-R^6 or O-CO-NH-R^6;
R^5 = H or a C_{1-6} alkyl chain which is unbranched or branched and which is substituted with one or more OH-groups;
R^6 = H, a C_{1-5} alkyl chain or R^5.

[0021] Especially preferred are the compounds 13, 14 and 18 shown in figure 6 and 7 and in Examples 10, 11 and 14 respectively.
[0022] The Q groups named above can be defined as C-groups and they have neither electron donor nor electron acceptor properties, and thus will be located within a limited area in figure 8, appendix 1.
[0023] Another aspect of the invention are compounds that release or decompose to active X-ray contrast agents of structure type A as previously defined.
[0024] A further aspect of this invention is novel iodinated alkenes. These chemical compounds can also be described by structure A, where Y is as defined above. The compounds are further characterised by:

R^1 = H, I, CH_2OH or R^3;
R^2 = H, I or R^3;
R^3 = CH_2-R^4, CH_2-R^5, $CH(R^4)_2$, CHR^4R^5, $CR^4(R^5)_2$ or R^5;
R^4 = O-R^5, O-$(CH_2CH_2$-O$)_{2-7}$-R^6, NH-CO-R^6, NH-CO-O-$(CH_2CH_2$-O$)_{1-6}$-R^6, NH-CO-O- R^6 or NB-CO-NH_2;
R^5 = a C_{3-8} alkyl chain which is unbranched or branched and which is substituted with one or more OH-groups;
R^6 = H, a C_{2-7} alkyl chain or R^5.

[0025] Preferred such compounds have:

R^2 = H, I or R^3;
R^3 = CH_2-R^4, CH_2-R^5, $CH(R^4)_2$, CHR^4R^5,R^5;
R^4 = O-R^5, O-$(CH_2CH_2$-O$)_{2-7}$-R^6, NH-CO-R^6, or NH-CO-O-R^6;
R^5 = a C_{3-7} alkyl chain which is unbranched or branched and which is substituted with one or more OH-groups.
R^6 = H, a C_{2-6} alkyl chain or R^5.

[0026] More preferred such compounds have:

R^3 = CH_2-R^4 or CH_2-R^5;
R^4 = O-R^5 or O-$(CH_2CH_2$-O$)_{2-7}$-R^6;
R^5 = a C_{3-6} alkyl chain which is unbranched or branched and which is substituted with one or more OH-groups.
R^6 = H, a C_{2-5} alkyl chain or R^5.

[0027] Especially preferred are the compounds 13, 14 and 18 shown in Figures 6 and 7 and in Examples 10, 11 and 14 respectively.
[0028] It has further been found that the synthetic route for the preparation of iodoalkenes of structure A is simpler and has fewer steps than the synthesis of conventional aromatic X-ray contrast agents. Possible important advantages of these syntheses are e.g. reduction of equipment, process time and costs relative to the synthesis of conventional aromatic X-ray contrast agents.
[0029] Possible synthetic routes to iodoalkenes according to this invention are summarised in figures 5, 6 and 7. The iodoalkenes are preferably prepared by iodination of substituted alkynes, as e.g. the synthesis of compound 6 from compound 4 shown in figure 5. The hydrophilic groups may alternatively be bound to iodoalkenes in the last step, see

e.g. the synthesis of compound 6 from compound 3.

[0030] A further aspect of the present invention is the use of the novel iodinated alkenes decsribed above as X-ray contrast agents.

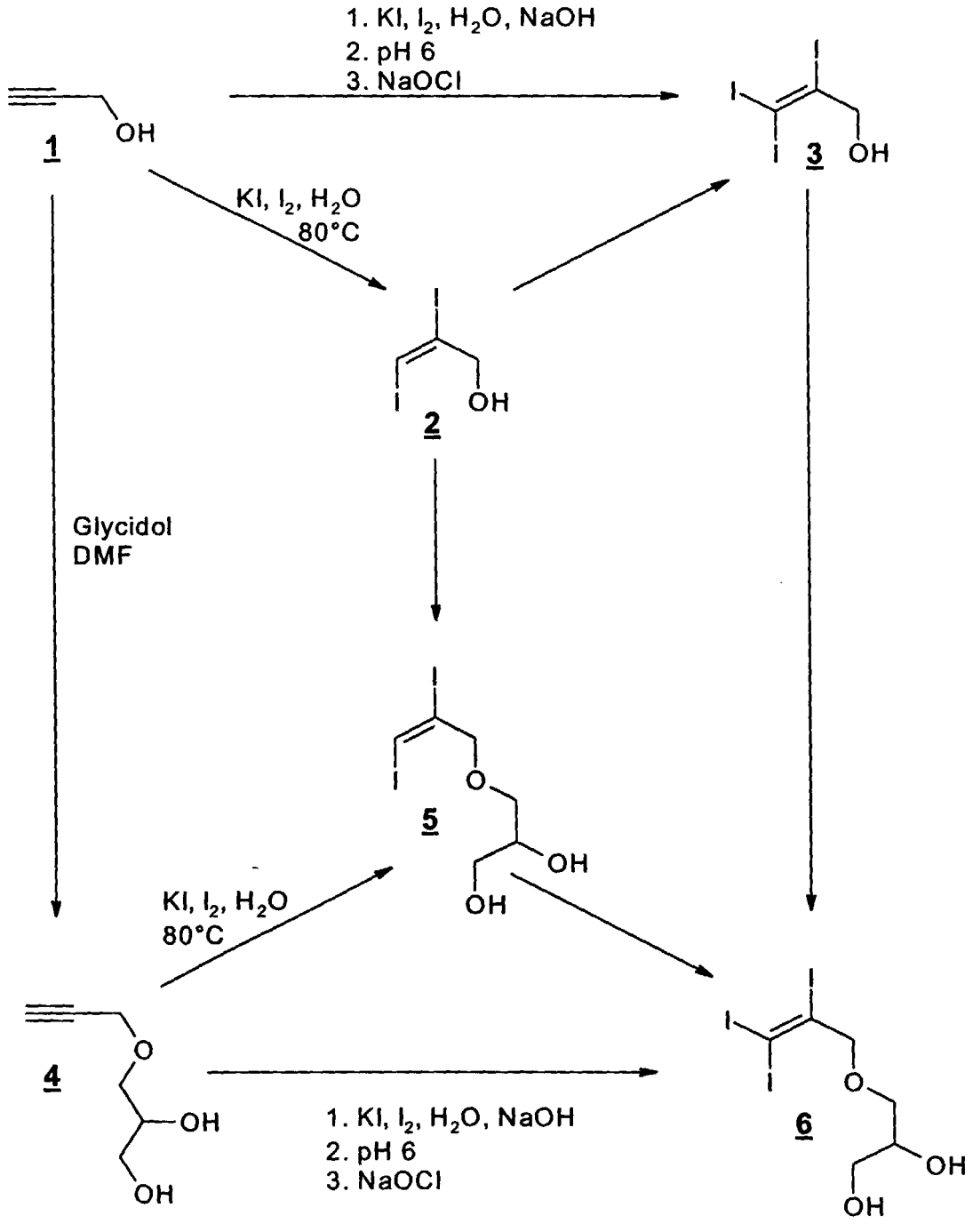


Figure 5: Structures and synthetic routes to iodoalkenes 2, 3, 5 and 6

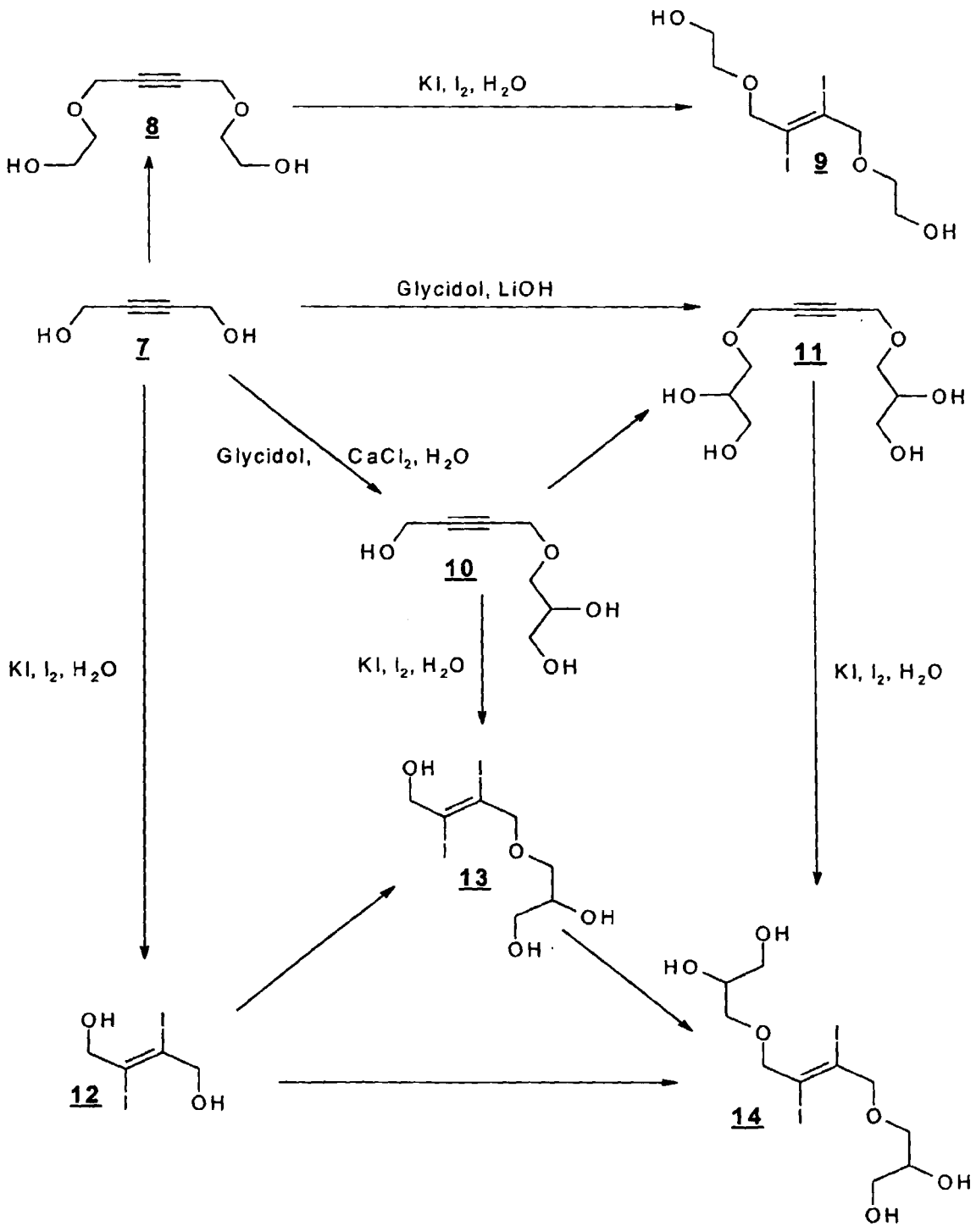


Figure 6: **Structures and synthetic routes to iodoalkenes 9, 12, 13 and 14**

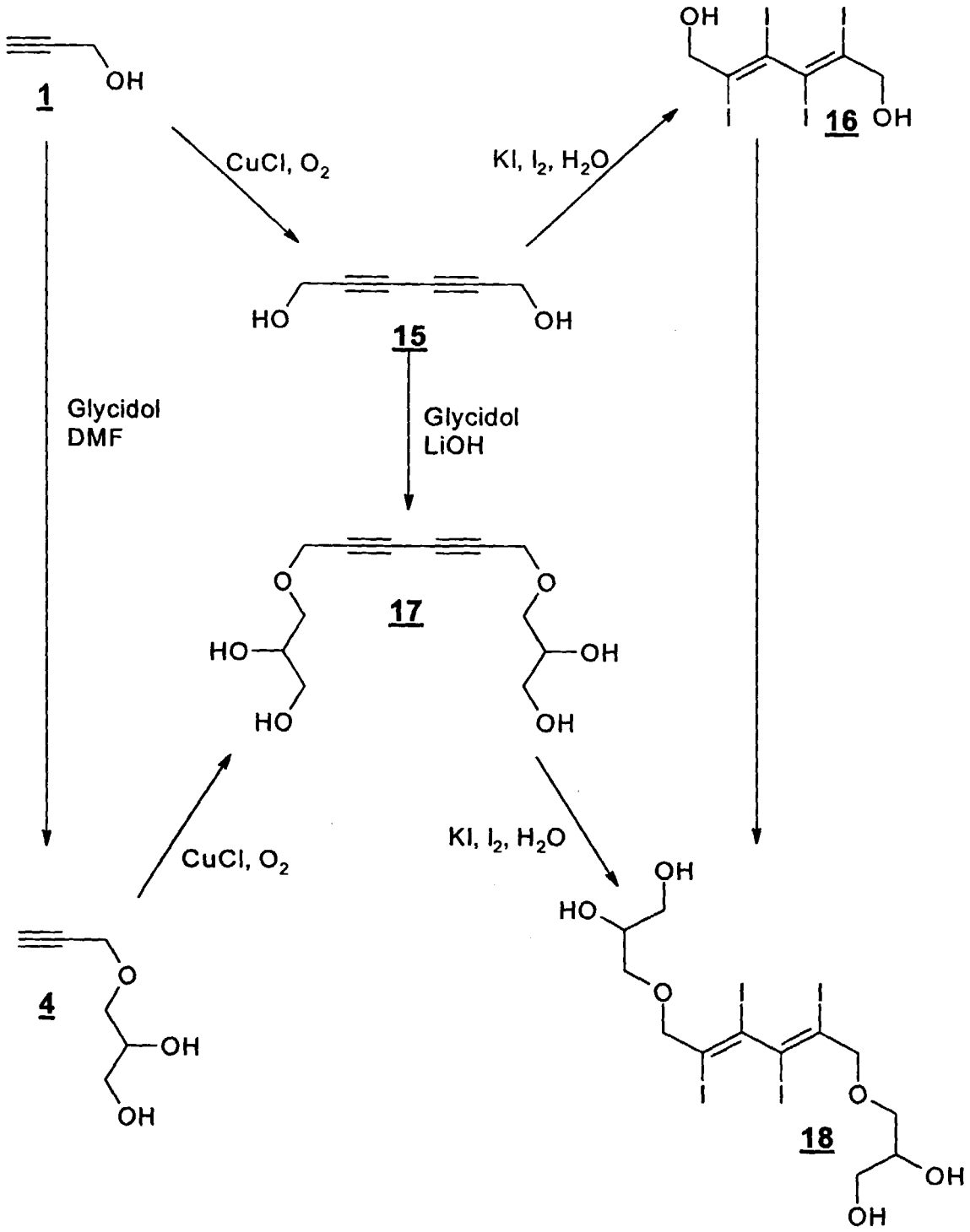


Figure 7: Structures and synthetic routes to iodoalkenes 16 and 18

[0031] The present invention therefor also includes a process for the preparation of iodinated alkenes with formula A by using the synthetic routes given in figure 5, 6 and 7. The iodination steps are described in examples 4, 5, 6, 10, 11 and 14. The iodination of alkynes is carried out in water as a cheap and environmentally friendly solvent.

[0032] The present invention also includes new processes for the preparation of hydrophilic alkynes as precursors to iodoalkenes with structure A. The preparation of compounds 4, 10, 11 and 17 is shown in figures 5, 6 and 7 and is

described in examples 3, 7, 8 and 13 respectively. The hydrophilic alkynes 4, 10 and 11 and other equivalent alkynes were prepared by O-alkylation of an alkynol with glycidol or glycidol analogues.

[0033] The invention also includes the use of compounds given by structure A as X-ray contrast agent. The compounds may be formulated with conventional carriers and solvents, e.g. water, in order to produce a diagnostic X-ray contrast agent.

[0034] Seen from another aspect, the present invention therefor provides a diagnostic composition consisting of a compound of structure A (as defined above) together with at least one physiologically acceptable carrier or solvent, e.g. in aqueous solution for injection, eventually with added plasma ions or dissolved oxygen. For use as an X-ray contrast agent it is advantageous to treat the compounds according to the invention by sterile filtration instead of autoclaving. X-ray contrast agents according to the invention can be produced in "ready for use" concentrations or can be formulated in concentrated form for dilution prior to administration. Compositions in "ready for use" form will typically have iodine concentrations of at least 100 mgI/ml, preferably at least 150 mgI/ml, and most preferably at least 300 mgI/ml. Effective ion concentrations can be obtained with isotonic solutions, and it may be desirable to obtain an isotonic solution by addition of plasma ions. Examples of possible plasma ions are ions of sodium, calcium, potassium and magnesium. Plasma ions can be present as counter ions in ionic contrast agents or they can be present in form of salts with physiologically acceptable counter ions, e.g. chloride, sulfate, phosphate, hydrogen carbonate and so on. In addition to plasma cations, the X-ray contrast agent may comprise other counter ions e.g. alkaline and alkaline earth metal ions, ammonium, meglumine, ethanolamine, diethanolamine, chloride, phosphate and hydrogen carbonate. Other counter ions conventionally used in pharmaceutical formulations may also be used. The formulation may in addition also contain other components used in pharmaceutical formulations, e.g. buffers.

[0035] In a further aspect, the invention provides a method of generating an X-ray image of a human being or an animal, preferably a human being, wherein the method is characterised by administration of a contrast agent according to the invention and generation of an X-ray image.

[0036] The following mono-, di-, tri- and tetra-iodinated model compounds are examples of compounds that can be used as X-ray contrast agents according to this invention, some as water-soluble and others as non-water soluble agents. Water-soluble agents are preferred.

	2-Iodo-2-propene-1-ol
	3-Iodo-2-propene-1ol, E- and/or Z- isomer
	3-(2-Iodo-2-propenyloxy)-propane-1,2-diol
	2-Iodo-2-butene-1,4-diol, E- and/or Z- isomer
	2-[(2,3-Diiodo-4-hydroxy-2-butenyl)oxy]-ethanol
2	2,3-Diiodo-2-propene-1-ol
3	2,3,3-Triiodo-2-propene-1-ol
5	3-(2,3-Diiodo-2-propenyloxy-propane-1,2-diol
6	3-(2,3,3-Triiodo-2-propenyloxy)-propane-1,2-diol
9	2,2'-[2,3-Diiodo-2-butene-1,4-diylbis(oxy)]-bis-ethanol
12	2,3-Diiodo-2-butene-1,4-diol
13	3-[(2,3-Diiodo-4-hydroxy-2-butenyl)oxy]-propane-1,2-diol
14	3,3'-[2,3-Diiodo-2-butene-1,4-diylbis(oxy)]-bis-propane-1,2-diol
16	2,3,4,5-Tetraiodo-2,4-hexadiene-1,6-diol
18	3-[6-(2,3-Dihydroxy-propoxy)-2,3,4,5-tetraiodo-hexa-2,4-dienyloxy]-propane-1,2-diol

[0037] According to the invention the following alkyne compounds can be used as precursors to iodoalkenes:

4	3-(2-Propynyloxy)-propane-1,2-diol

(continued)

8	1,4-Bis-(2-hydroxyethoxy)-2-butyne
10	3-[(4-Hydroxy-2-butynyl)oxy]-propane-1,2-diol
11	3,3'-[2-Butyne-1,4-diylbis(oxy)]-bis-propane-1,2-diol
17	3-[6-(2,3-Dihydroxy-propoxy)-hexa-2,4-diynyloxy]-propane-1,2-diol

[0038] According to the invention the following compounds can be used as catalysts under O-alkylation reactions of alkynols with glycidol or glycidol equivalents: $SOCl_2$, H_2SO_4, DMF, $CaCl_2$ and/or $CaCl_2*2H_2O$, Na_2HPO_4, K_3PO_4, 2,6-Dimethyl-pyridine, LiOH, NaOH, $Ca(OH)_2$, $NaOAc*3H_2O$.

[0039] According to the invention the following compounds can be used as glycidol equivalents under O-alkylation reactions together with equimolar amounts of base, e.g. NaOH, KOH, $Ca(OH)_2$:

3-Halo-propane-1,2-diol where halo = Cl, Br or I
2-Halo-propane-1,3-diol where halo = Cl, Br or I.

[0040] The aqueous solubilities (g/L) of certain compounds according to this invention are given in table 1.

Table 1

Aqueous solubilities of iodinated alkenes according to this invention		
Compound	Aqueous solubility at 20°C (g/L)	iodine content (%)
2	0.391	82
3	0.198	87
5	18.38	66
6	0.5	75
9	7.2	59
12	0.534	75
13	>1200	61
14	>1200	52
16	0.183	82
Iohexol	>1200	46

[0041] The invention is illustrated with reference to the following non-limiting examples:

Example 1: 2,3-diiodo-2-propene-1-ol (2); [71264-49-8]

[0042] 2 was synthesised from propargyl alcohol 1 as described by Iserson, H., Smith, H.Q., *US patent* 3,342,582, 19. sept. 1967. The crude product was recrystallised from water and gave 2 in 52 % yield. MP. 52 - 52.5°C (lit. 51.5 - 52.5). TLC on silica; EtAc:CH_3CN = 1:1; R_f = 0.69. Aqueous solubility at 20°C = 3.913 g/L.

Spectroscopic data:

[0043]

MS [m/z, (% rel. int), fragment]: 310.2 (63) M, 254.1 (10) I_2, 183.1 (100) M-I, 127.0 (21) I, 56.1 (7) M-2I, 55.1 (40) M-(2I+H).
IR [ν^{KBr}, cm^{-1}]: 4268 (w), 3690 (w), 3251 (s, broad, O-H), 3058 (s, =C-H), 2949 (m, C-H), 2912 (m, C-H), 2839 (m, C-H), 2694 (m), 2426 (w), 2081 (w), 1710 (w), 1563 (m, C=C), 1435 (s, CH_2), 1353 (m, CO-H), 1242 (m, CH_2 + CO-

H), 1218 (s, CO-H), 1074 (m, C-OH), 1051 (s, C-OH), 1018 (m, C-OH), 1009 (s, C-OH), 958 (s, C-OH), 783 (s, =C-H), 633 (s, =C-H), 586 (m), 531 (s).

^{1}H-NMR [300 MHz, $CDCl_3$]: δ 2.56 (1H, s, OH), 4.29 (2H, d, J = 0.92 Hz, CH_2), 7.05 (1H, t, $^4J_{HH}$ = 0.9 Hz, =CH-) ppm.

^{13}C-NMR [300MHz, $CDCl_3$]: δ 70.62, 79.91, 104.10 ppm.

UV [MeOH]: λ_{max} = 238.4 nm.

Example 2: 2,3,3-triiodo-2-propene-1-ol (3); [42778-72-3]

[0044] 3 was synthesised from propargyl alcohol 1 as described by Gerhardt, W., Hase, C., *DE patent* 3142654, 28. oct. 1981. The crude product was recrystallised from H_2O:EtOH = 1:1 and gave 3 in 81 % yield. MP. 153.5 - 154.0°C (lit.: 145 - 148°C). TLC on silica; EtAc, R_f = 0.65. Aqueous solubility at 20°C = 0.198 g/L.

Spectroscopic data:

[0045]

MS [m/z, (% rel. int.), fragment]: 435.8 (100) M, 308.9 (91) M-I, 253.9 (18) I_2, 182.0 (21) M-2I, 127.0 (56) I, 55.0 (27) M-3I, 54 (11) M-(3I+H).

IR [ν^{KBr}, cm^{-1}]: 3193 (s, broad, O-H), 2938 (m, C-H), 2920 (m, C-H), 2861 (m, C-H), 2813 (m, C-H), 2625 (w), 2434 (w), 1548 (m, C=C), 1445 (m, CH_2), 1410 (m, CH_2), 1345 (w, CO-H), 1220 (m, CO-H), 1051 (s, C-OH), 1024 (s, C-OH), 964 (s, C-OH), 764 (m), 736 (m), 602 (m), 553 (m), 407 (m).

^{1}H-NMR [300 MHz, DMSO]: δ 4.01 (2H, d, J = 6.2 Hz, CH_2), 5.65 (2H, t, J = 6.2 Hz, OH) ppm.

^{13}C-NMR [300 MHz, DMSO]: δ 28.30, 72.93, 122.03 ppm.

UV [MeOH]: λ_{max} = 202.6 nm

Example 3: 3-(2-propynyloxy)-propane-1,2-diol (4); [13580-38-6]

[0046] 4 was synthesised from propargyl alcohol 1 and glycidol in DMF. 2-Propyne-1-ol (56.06 g, 1.0 mol) and DMF (0.56 g, 0.01 mol) were heated to 110°C under stirring. Glycidol (67.30 g, 0.91 mol) was added dropwise within one hour (exothermic reaction!) keeping the temperature in the flask below 150°C. After 3 hours the mixture was cooled to room temperature. The crude product, approx. 95 g of a dark orange oil was distilled in a kugelrohr-distillation apparatus under vacuum and gave 60.2 g of 4 as a slight yellowish oil in 51 % yield. BP. 92°C/~1mbar, n_D^{20} = 1.4759 (lit. n_D^{20} = 1.4761). TLC on silica; EtAc, R_f = 0.27, The TLC plate needs development in an iodine chamber for visualisation of 4.

Spectroscopic data:

[0047]

MS [m/z, (% rel. int.), fragment]: 152.8 (100) M + Na.

IR [ν^{KBr}, cm^{-1}]: 3953 (w), 3361 (s, broad, OH), 3293 (s, C-H), 2933 (m, C-H), 2878 (m, C-H), 2116 (m, C C), 1441 (m, CH_2), 1360 (m, CO-H), 1269 (m, CH_2 + CO-H), 1100 (s, C-O-C), 1037 (s, C-OH), 956 (m), 864 (m), 668 (m), 543 (m).

^{1}H-NMR [300 MHz, $CDCl_3$]: δ 2.51 (1H, t, $^4J_{HH}$ = 2.4 Hz, CH), 3.52 - 3.74 (6H, m, CH-OH, CH_2-OH), 3.86 - 3.98 (1H, m, CH_2-O), 4.20 (2H, d, $^4J_{HH}$ = 2.4 Hz, CH_2-O) ppm.

^{13}C-NMR [300 MHz, $CDCl_3$]: δ 58.60, 63.80, 70.74, 71.26, 75.04, 79.36 ppm.

UV [MeOH]: λ_{max} = 264.9 nm.

Example 4: 3-(2,3-diiodo-2-propenyloxy)-propane-1,2-diol (5)

[0048] 3-(2-propynyloxy)-propane-1,2-diol (4, 11.73 g, 0.09 mol) was added to a solution of KI (13.28 g, 0.08 mol) and I_2 (22.85 g, 0.09 mol) in water (400 ml). The reaction mixture was heated under reflux for 3 hours. The reaction mixture separated into two layers. The lower brown-black organic phase was separated, 28.4g. The water phase was extracted with diethyl ether (2x100 ml) and the ether phase was evaporated, 4.04 g. The combined organic phases were purified by flash chromatography on silica with ethyl acetate as eluent. 29.2 g of 5 was collected in 84.5 % yield. The light yellow oil crystallised in the refrigerator during the night and gave a light yellow solid. MP. 33-36°C. TLC on silica; EtAc, R_f = 0.44; MeAc, R_f = 0.68. Aqueous solubility at 20°C = 18.38 g/L.

Spectroscopic data:

[0049]

MS [m/z, (% rel. int), fragment]: 384.0 (0.3) M, 292.9 (76) $C_3H_3I_2$, 257.0 (26) M-I, 253.9 (17) I_2, 183.0 (92) C_3H_4IO, 130.1 (5) M-2I, 129.1 (13) M - (2I+H), 128.0 (32) M - (2I+2H), 127.0 (21) I, 75.1 (100) $C_3H_7O_2$.
IR [ν^{KBr}, cm^{-1}]: 4268 (w), 4010 (w) 3409 (s, broad, O-H), 3052 (m, =C-H), 2925 (m, C-H), 2439 (w), 1582 (w), 1440 (m, CH_2), 1343 (m, CO-H), 1262 (m, CH_2 + CO-H), 1221 (s, CO-H), 1126 (s, C-O-C), 1105 (s, C-OH), 1043 (s, C-OH), 1011 (m, C-OH), 977 (m), 934 (m), 850 (m), 782 (s), 702 (m), 639 (m), 542 (m).
^{1}H-NMR [300 MHz, DMSO]: δ 3.25 - 3.43 (4H, m, CH_2-O, CH_2-OH), 3.5 - 3.7 (1H, m, CH-OH), 4.15 (2H, t, $^4J_{HH}$ = 0.8 Hz, CH_2-O), 4.53 (1H, t, $^3J_{HH}$ = 5.6 Hz, prim. OH), 4.72 (1H, d, $^3J_{HH}$ = 5.1 Hz, sec. OH), 7.45 (1H, t, $^4J_{HH}$ = 0.8 Hz, =CH) ppm.
^{13}C-NMR [300 MHz, DMSO]: δ 63.07, 70.29, 71.25, 77.19, 84.71, 101.77 ppm.
UV [MeOH]: λ_{max} = 240.0 nm.

Example 5: 3-(2,3,3-triiodo-2-propenyloxy)-propane-1,2-diol (6)

[0050] To a stirred solution of 3-(2-propynyloxy)-propane-1,2-diol (4, 13.09 g, 0.1 mol) in H_2O (40 ml) at 0°C was added NaOH (4.04 g, 0.1 mol) and KI (49.81 g, 0.3 mol). 14% aqueous NaOCl (53.01 g, 0.1 mol) was added dropwise over a 1.5 hour period in order to keep the flask temperature between 0 and 10°C. During 30 min a part of 50 % aqueous H_2SO_4 (53.18 g, 0.27 mol) was added dropwise until pH~2, keeping the mixture temperature between 5 an 15°C. The rest of the acid was added simultaneous with 14 % aqueous NaOCl (53.01 g, 0.1 mol) during 1.5 hours. The reaction mixture was stirred at room temperature over night. The brown-black lower organic phase (47 g) was separated and the aqueous phase extracted with EtAc (2x50 ml). The EtAc phase was evaporated to dryness, 3 g. The combined organic phases (50 g crude product) crystallised during the night in the refrigerator. The crude product was recrystallised from H_2O:EtOH (9:1) and kept at 4°C over night. The substance precipitated from the solution, was filtered and dried. This gave 38.8 g 6 as a slight yellow cotton like solid in 76% yield. MP. 70 - 71.5°C. TLC on silica; EtAc, R_f = 0.48. Aqueous solubility at 20°C = 0.5 g/L.

Spectroscopic data:

[0051]

MS [m/z, (% rel.int.) fragment]: 435.0 (3) $C_3H_2I_3O$, 419.1 (32) $C_3H_2I_3$, 383.2 (25) M-I, 309.1 (91) $C_3H_3I_2O$, 293.1 (13) $C_3H_3I_2$, 256.1 (2) M-2I, 255.1 (17) M-(2I+H), 254 (95) I_2, 181.1 (9) C_3H_2IO, 165.1 (100) C_3H_2I, 129.2 (2) M-3I, 128.0 (23) M-(3I+H), 127.0 (31) I, 75.1 (72) $HOCH_2CH_2OH$.
IR [ν^{KBr}, cm^{-1}]: 3365 (m, broad, O-H), 3230 (m, O-H), 2966 (m, C-H), 2901 (m, C-H), 1538 (w), 1464 (m, CH_2), 1385 (m, CO-H), 1342 (m, CO-H), 1269 (m, CH_2 + CO-H), 1245 (m, CH_2 + CO-H), 1218 (w), 1121 (s, C-O-C), 1082 (s, C-OH), 1066 (s, C-OH), 1024 (m, C-OH), 981 (m), 936 (m), 895 (m), 840 (m), 731 (m), 706 (m), 608 (m), 529 (m), 486 (m), 419 (w).
^{1}H-NMR [300 MHz, DMSO]: δ 3.24 - 3.44 (4H, m, CH_2-O, CH_2-OH), 3.54 - 3.64 (1H, m, CH-OH), 4.12 (2H, s, CH_2-O), 4.50 (1H, t, $^3J_{HH}$ = 5.7 Hz, prim. OH), 4.69 (1H, d, $^3J_{HH}$ 5.2 Hz, sec. OH) ppm.
^{13}C-NMR [300 MHz, DMSO]: δ 23.41, 63.08, 70.32, 71.23, 80.83, 116.83 ppm.

Example 6: 2,2'-[2,3-diiodo-2-butene-1,4-diylbis(oxy)]-bis-ethanol (9)

[0052] 1,4-bis-(2-hydroxyethoxy)-2-butyne (8, 87.12 g, 0.50 mol) was added to a solution of KI (172.04 g, 1.04 mol) and I_2 (129.51 g, 0.51 mol) in water (1500 ml). The reaction mixture was heated under reflux for 3 hours and stirred at room temperature over night. The lower brown-black organic phase was separated and the aqueous phase was extracted with diethyl ether. The combined organic phases were evaporated and gave 289 g crude product. 7 g of the crude product were purified by preparative HPLC (RP-18 column with H_2O:CH_3CN = 8:2). This gave 1.7 g of 9 as a slight yellow cotton like solid in 24 % yield. MP. 79-82°C. TLC on silica; EtAc:CH_3CN = 1:1, R_f = 0.52. Aqueous solubility at 20°C = 7.2 g/L.

Spectroscopic data:

[0053]

MS [m/z, (% rel.int.) fragment]: 451 (100) M+Na, 429 (8) M+H.
IR (ν^{KBr}, cm^{-1}): 3306 (m, broad, O-H), 3204 (m, bred, O-H), 2932 (m, C-H), 2862 (m, C-H), 1497 (w), 1435 (m, CH_2), 1344 (m, CO-H), 1285 (w), 1266 (m, CH_2 + CO-H), 1208 (m, CO-H), 1119 (s, C-O-C), 1057 (s, C-OH), 996 (m, C-OH), 902 (s, C-OH), 831(m), 666 (m), 533 (w), 484 (m).
^{1}H-NMR [300 MHz, DMSO]: δ 3.38 - 3.58 (8H, m, CH_2-CH_2-OH), 4.37 (4H, s, CH_2-O), 4.64 (2H, t, $^3J_{HH}$ = 5.5 Hz, OH) ppm.
^{13}C-NMR [300 MHz, DMSO]: δ 59.93, 70.92, 81.68, 103.32 ppm.

Example 7: 3-[(4-Hydroxy-2-butynyl)oxy]-propane-1,2-diol (10); [81748-55-2]

[0054] At room temperature glycidol (23.28 g, 0.317 mol) was added to 2-butyne-1,4-diol (7, 18.11 g, 0.21 mol) and stirred until the mixture became homogeneous. A solution of $CaCl_2$ (35.18 g, 0.317 mol) in H_2O (65 ml) was added. The reaction was exothermic and the mixture turned yellow and more viscous. After the generation of heat stopped the reaction mixture was stirred at 50°C for 6 hours. TLC on silica; EtAc:EtOH = 9:1, (10) R_f = 0.24, (7) R_f = 0.46. The mixture was used directly in the following iodination reaction to (13), see example 10.

Example 8: 3,3'-[2-butyne-1,4-diylbis(oxy)]-bis-propane-1,2-diol (11) [81748-56-3]

[0055] At room temperature glycidol (32.52 g, 0.44 mol) was added to 2-butyne-1,4-diol (7, 18.11 g, 0.21 mol) and stirred until the mixture became homogeneous. LiOH (0.024 g, 0.001 mol) was added and the reaction mixture was stirred at 50°C for 6 hours. TLC on silica; EtAc:EtOH = 9:1, (11) R_f = 0.11, (10) R_f = 0.24, (7) R_f = 0.46. The mixture was used directly in the following iodination reaction to (14), see example 11.

Example 9: 2,3-diiodo-2-butene-1,4-diol (12); [19095-64-8] & [62994-00-7]

[0056] 12 was synthesised from 2-butyne-1,4-diol (7) as described by Iserson,H., Smith, H.Q., *US patent* 3,342,582, 19. Sept. 1967. The crude product was recrystallised from water and gave 12 in 93 % yield. MP. 179.5-180.5°C (lit. 179-180°C). TLC on silica; EtAc:CH_3CN = 1:1, R_f = 0.70; EtAc:EtOH = 9:1, R_f = 0.67. Aqueous solubility at 20°C = 0.534 g/L.

Spectroscopic data:

[0057]

MS [m/z, (% rel. int), fragment]: 340.1 (97) M, 253.9 (7) I_2, 195 (100) M-(H_2O+I), 127.0 (19) I, 86.1 (93) M-2I, 68.1 (40) M-(H_2O+2I).
IR [ν^{KBr}, cm^{-1}]: 3212 (s, broad, O-H), 2932 (m, C-H), 2919 (m, C-H), 2863 (m, C-H), 2826 (m, C-H), 2639 (w), 2560 (w), 2448 (w), 2089 (w), 2022 (w), 1448 (m, CH_2), 1419 (m, CH_2), 1350 (m, CO-H), 1231 (m, CH_2 + CO-H), 1075 (s, C-OH), 1069 (s, C-OH), 1010 (s, C-OH), 999 (s, C-OH), 755 (m), 609 (m), 526 (m).
^{1}H-NMR [300 MHz, DMF]: δ 4.36 (4H, s, CH_2), 5.60 (2H, s, OH) ppm.
^{13}C-NMR [300 MHz, DMF]: δ 75.22, 105.10 ppm.
UV [MeOH]: λ_{max} = 238.8 nm.

Example 10: 3-[(2,3-diiodo-4-hydroxy-2-butenyl)oxy)]-propane-1,2-diol (13)

[0058] The reaction mixture of 10 (0.21 mol) from example 7 was added to a solution of KI (70.20 g, 0.423 mol) and I_2 (53.55 g, 0.211 mol) in H_2O (550 ml). The mixture was heated under reflux for 3.5 hours. 20 % aqueous $Na_2S_2O_5$ was added to the dark reaction mixture until no further reduction in colour was observed (total added 15 ml). The light yellow suspension was filtered to remove precipitated 12 and the filtrate was concentrated to half the volume. The aqueous phase was extracted with MeAc (5x250 ml). The MeAc fractions were collected, filtered and evaporated to dryness. The residue was again extracted with MeAc (5x250 ml).). The MeAc fractions were collected, filtered and evaporated to dryness. This gave 21.4 g crude product.
15.6 g crude product were purified by chromatography on silica with gradient elution starting with EtAc and ending with EtAc:MeOH = 9:1. This gave 7.39 g (13) as a light brown, viscous oil. n_D^{18} = 1.638. TLC on silica; EtAc:EtOH = 9:1, R_f

= 0.44. Aqueous solubility at 20°C is greater than 1.2 g/L.

Spectroscopic data:

[0059]

MS [m/z, (% rel.int.) fragment]: 437 (100) M+Na.
IR (ν^{KBr}, cm^{-1}): 3386 (s, broad, O-H), 2911 (m, C-H), 2870 (m, C-H), 1710 (w), 1626 (w), 1442 (m, CH_2), 1351 (m, CO-H), 1235 (m, CH_2 + CO-H), 1110 (s, C-O-C), 1056 (s, C-OH), 955 (m), 927 (m), 865 (m).
^{1}H-NMR [300 MHz, DMSO]: δ 3.24 - 3.46 (4H, m, CH_2-O), 3.56 - 3.66 (1H, m, CH-O), 4.22 (2H, d, $^3J_{HH}$ = 6.0 Hz, CH_2-C=), 4.35 (2H, s, CH_2-C=), 4.49 (1H, s, $^3J_{HH}$ = 5.6 Hz, prim. OH), 4.68 (IH, s, $^3J_{HH}$ = 5.1 Hz, sec. OH), 5.59 (1H, t, $^3J_{HH}$ = 6.0 Hz, prim. OH) ppm.
^{13}C-NMR [300 MHz, DMSO]: δ 63.15, 70.36, 71,22, 73.70, 82.07, 99.44, 108.77 ppm.

Example 11: 3,3'-[2,3-diiodo-2-butene-1,4-diylbis(oxy)]-bis-propane-1,2-diol (14)

[0060] The reaction mixture of 11 (0.21 mol) from example 8 was added to a solution of KI (69.45 g, 0.42 mol) and I_2 (53.06 g, 0.21 mol) in H_2O (645 ml). The mixture was heated under reflux for 3.5 hours. 20 % aqueous $Na_2S_2O_5$ was added to the dark reaction mixture until no further reduction in colour was observed (total added 20 ml). The light yellow suspension was filtered to remove precipitated 12 and the filtrate was evaporated to dryness. The residue was resuspended in MeOH (400 ml). Insoluble inorganic salts were filtered and the filtrate was evaporated to dryness, yielding ca. 180 g crude product. A minor part of the crude product was purified by preparative HPLC (RP-18 column with H_2O:CH_3CN = 9:1). This gave 1.3 g 14 as a light yellow cotton like solid. MP. 80.5 - 82.5°C. TLC on silica; EtAc:EtOH = 9:1, R_f = 0.25. Aqueous solubility at 20°C is greater than 1.2 g/L.

Spectroscopic data:

[0061]

IR (ν^{KBr}, cm^{-1}): 3355 (s, broad, O-H), 2898 (m, C-H), 2866 (m, C-H), 1448 (m, CH_2), 1347 (m, CO-H), 1246 (m, CH_2 + CO-H), 1125 (s, C-O-C), 1051 (s, C-OH), 1009 (s, C-OH), 928 (m), 850 (w), 827 (w), 665 (w), 611(w), 568 (w), 533 (m).
^{1}H-NMR [300MHz, DMSO]: δ 3.27 - 3.44 (8H, m, CH_2-O), 3.56 - 3.66 (2H, m, CH-O), 4.37 (4H, s, CH_2-C=), 4.49 (2H, t, $^3J_{HH}$ = 5.6 Hz, prim. OH), 4.67 (2H, d, $^3J_{HH}$ = 5.6 Hz, sec. OH) ppm.
^{13}C-NMR [300MHz, DMSO]: δ 63.10, 70.34, 71.27, 81.94, 103.17 ppm.

Example 12: 2,3,4,5-tetraiodo-2,4-hexadiene-1,6-diol (16); [13231-82-8]

[0062] 16 was synthesised from 2,4-hexadiyne-1,6-diol (15) as described by Iserson, H., Smith, H.Q., *US patent* 3,342,582, 19. sept. 1967, but the work up was done in a different way. The crude product was purified by flash chromatography on silica with EtAc as eluent and recrystallised from *i*-PrOH/H_2O (1:2). This gave 16 as orange crystals in 43 % yield. MP. 94 - 96°C (lit. 95 - 96°C). TLC on silica; EtAc:CH_3CN = 1:1; R_f = 0.73. Aqueous solubility at 20°C = 0.183 g/L.

Spectroscopic data:

[0063]

MS [m/z, (% rel. int), fragment]: 490.8 (30) M-I, 363.9 (25) M-2I, 253.8 (100) I_2, 237.0 (5) M-3I, 127.0 (41) I, 110.9 (20) M-4I.
IR [ν^{KBr}, cm^{-1}]: 4360 (w), 3529 (m, OH), 3258 (s, broad, OH), 2917 (m, C-H), 2869 (m, C-H), 2682 (w), 1684 (w, conj. C=C), 1623 (w, conj. C=C), 1560 (w), 1528 (w), 1426 (m, CH_2), 1354 (m, CO-H), 1233 (m, CH_2 + CO-H), 1055 (s, C-OH), 1027 (s, C-OH), 998 (m), 963 (m), 936 (m), 700 (m), 650 (m), 590 (m), 562 (m).
^{1}H-NMR [300 MHz, DMSO]: δ 4.09 (4H, s, CH_2), 5.66 (2H, s, OH) ppm.
^{13}C-NMR [300 MHz, DMSO]: δ 72.18, 103.05, 110.54 ppm.

Example 13: 3-[6-(2,3-Dihydroxy-propoxy)-hexa-2,4-diynyloxy]-propane-1,2-diol (17)

[0064] An aqueous NH_4Cl solution was saturated at 5°C. CuCl (1.0 g, 18,7 mmol) was added to 20 ml of the saturated aqueous NH_4Cl solution. The reaction vessel was filled with O_2 and the mixture was vigorously stirred during the whole reaction time. 3-(2-propynyloxy)-propane-1,2-diol (4, 13,01 g, 100 mmol) was added at room temperature in 5 portions during 2.5 hours. The reaction mixture was stirred at 40° for 1 hour and then evaporated to dryness. The residue was dissolved in 50 ml $CH_3CN:H_2O$ = 1:1 and filtered through 20 g silica 60. The filter column was washed with 100 ml $CH_3CN:H_2O$ = 1:1 and the filtrate was evaporated to dryness. The residue was suspended in MeOH (70 ml) and insoluble inorganic components removed by filtration. The filtrate was diluted with water (500 ml) and stirred with ion exchangers (IRA 67, 110ml; AMB 200C, 110 ml) and activated carbon (0.1 g). The ion exchangers were filtered off and washed with water (2x250ml). The combined filtrates were evaporated and gave 9.8 g 17 as a light yellow oil in 76 % yield. TLC on silica; $H_2O:CH_3CN$ = 1:1, R_f = 0.79; CH_3CN, R_f = 0.26.

Spectroscopic data:

[0065]

MS [m/z, (% rel. int.), fragment]: 259 (6) M+H, 167 (100) M-[CH_2-O-CH_2-CH(OH)-CH_2OH].
IR [ν^{KBr}, cm^{-1}]: 3381 (s, broad, OH), 2934 (m, C-H), 2880 (m, C-H), 2115 (w, C C), 1401 (m, CH_2), 1352 (m, CO-H), 1263 (m, CH_2 + CO-H), 1089 (s, C-O-C), 1035 (s, C-OH), 950 (m), 864 (m), 673 (m), 556 (m).
^{1}H-NMR [300 MHz, DMSO]: δ 3.30 - 3.50 (8H, m, CH_2-O), 3.56 - 3.62 (2H, m, CH-O), 4.20 (4H, s, CH_2-O), 4.52 (2H, t, prim. OH), 4.72 (2H, d, sec. OH) ppm.
^{13}C-NMR [300 MHz, DMSO]: δ 58.12, 62.83, 69.38, 71.75, 76.65 ppm.

Example 14: 3-[6-(2,3-Dihydroxy-propoxy)-2,3,4,5-tetraiodo-hexa-2,4-dienyloxy]-propane-1,2-diol (18)

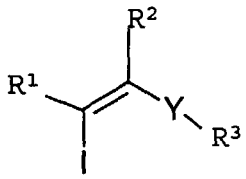
[0066] The reaction mixture of 17 (8.0 g, 31 mmol) from Example 13 was added to a solution of KI (20.57 g, 0.123 mol) and I_2 (15.72 g, 62 mmol) in H_2O (300 ml). The mixture was heated to 70°C for 2 hours and was stirred over night at room temperature. 37 % aqueous $NaHSO_3$ was added to the dark reaction mixture until no further reduction in colour was observed (total added 40 ml). The reaction mixture was evaporated to dryness. The residue was suspended in MeOH (150 ml). Insoluble inorganic salts were filtered off and the filtrate was evaporated to dryness, yielding ca. 40 g crude product. The residue was suspended in EtOH (200 ml). Insoluble inorganic salts were filtered off and the filtrate was evaporated to dryness, yielding ca. 30 g crude product.

TLC on silica; CH_3CN, R_f = 0.62.

The crude product was purified by preparative HPLC (RP-18 column with $H_2O:CH_3CN$ = 9:1).

Claims

1. An X-ray contrast composition which comprises a compound of formula A:



A

wherein:

Y = $(IC{=}CI)_n$ where n is 0 or 1;
R^1 and R^2 are independently I or Q;
R^3 is Q;

where each Q is the same or different, and is an electronically neutral substituent which preferably has a resonance effect R and field/inductive effect F in the range: $0.06 \geq R \geq -0.45$ and $0.24 \geq F \geq -0.03$.

2. The X-ray contrast composition of claim 1, where the Q groups each have values for resonance effect R and field/inductive effect F in the range:

$0.04 \geq R \geq -0.39$ and $0.22 \geq F \geq -0.02$.

3. The X-ray contrast composition of claim 1, where the Q groups each have values for resonance effect R and field/inductive effect F in the range:

$0.02 \geq R \geq -0.33$ and $0.20 \geq F \geq -0.01$.

4. The X-ray contrast composition of claim 1, wherein:

R^1 = H, I, CH_2OH or R^3;
R^2 = H, I, CH_2OH or R^3;
R^3 = H, CH_2-R^4, CH_2-R^5, $CH(R^4)_2$, CHR^4R^5, $CR^4(R^5)_2$, R^5 or $(CH_2)_{1-3}$-CO-NR^5R^6;
R^4 = O-R^5, O-$(CH_2CH_2$-O$)_{1-7}$-R^6, NH-CO-R^6, NH-CO-O-$(CH_2CH_2$-O$)_{1-6}$-R^6, NH-CO-O-R^6, NH-CO-NH_2, O-CO-R^6, O-CO-O-R^6 or O-CO-NH-R^6;
R^5 = H, or a C_{1-8} alkyl chain which is unbranched or branched and which is substituted with one or more OH-groups.
R^6 = H, a C_{1-7} alkyl chain or R^5.

5. The X-ray contrast composition of claim 4 wherein:

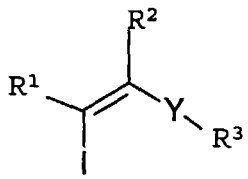
R^3 = H, CH_2-R^4, CH_2-R^5, $CH(R^4)_2$, CHR^4R^5 or R^5;
R^4 = O-R^5, O-$(CH_2CH_2$-O$)_{1-7}$-R^6, NH-CO-R^6, NH-CO-O- R^6, O-CO-R^6, or O-CO-NH-R^6;
R^5 = H or a C_{1-7} alkyl chain which is unbranched or branched and which is substituted with one or more OH-groups;
R^6 = H, a C_{1-6} alkyl chain or R^5.

6. The X-ray contrast composition of claim 5 wherein:

R^3 = CH_2-R^4 or CH_2-R^5;
R^4 = O-R^5, O-$(CH_2CH_2$-O$)_{1-6}$-R^6, O-CO-R^6 or O-CO-NH-R^6;
R^5 = H or a C_{1-6} alkyl chain which is unbranched or branched and which is substituted with one or more OH-groups;
R^6 = H, a C_{1-5} alkyl chain or R^5.

7. The X-ray contrast composition of claims 1 to 6, further comprising a physiologically acceptable carrier or solvent.

8. Chemical compounds of formula A:



A

wherein:

Y = $(IC{=}CI)_n$ where n is 0 or 1;

R^1 = H, I, CH_2OH or R^3;
R^2 = H, I or R^3;
R^3 = CH_2-R^4, CH_2-R^5, $CH(R^4)_2$, CHR^4R^5, $CR^4(R^5)_2$ or R^5;
R^4 = O-R^5, O-$(CH_2CH_2$-O$)_{2-7}$-R^6, NH-CO-R^6, NH-CO-O-$(CH_2CH_2$-O$)_{1-6}$-R^6, NH-CO-O- R^6 or NH-CO-NH_2;
R^5 = a C_{3-8} alkyl chain which is unbranched or branched and which is substituted with one or more OH-groups;
R^6 = H, a C_{2-7} alkyl chain or R^5.

9. Compounds as claimed in claim 8 wherein

R^2 = H, I or R^3;
R^3 = CH_2-R^4, CH_2-R^5, $CH(R^4)_2$, CHR^4R^5, R^5;
R^4 = O-R^5, O-$(CH_2CH_2$-O$)_{2-7}$-R^6, NH-CO-R^6, or NH-CO-O- R^6;
R^5 = a C_{3-7} alkyl chain which is unbranched or branched and which is substituted with one or more OH-groups.
R^6 = H, a C_{2-6} alkyl chain or R^5.

10. Compounds as claimed in claim 9 wherein

R^3 = CH_2-R^4 or CH_2-R^5;
R^4 = O-R^5 or O-$(CH_2CH_2$-O$)_{2-7}$-R^6;
R^5 = a C_{3-6} alkyl chain which is unbranched or branched and which is substituted with one or more OH-groups.
R^6 = H, a C_{2-5} alkyl chain or R^5.

11. The compound

3-[6-(2,3-Dihydroxy-propoxy)-2,3,4,5-tetraiodo-hexa-2,4-dienyloxy]-propane-1,2-diol (18).

12. The compound 3,3'-[2,3-diiodo-2-butene-1,4-diylbis(oxy)]-bis-propane-1,2-diol (14).

13. The compound 3-[(2,3-diiodo-4-hydroxy-2-butenyl)oxy)]-propane-1,2-diol (13).

14. A process for the preparation of the iodoalkene of claims 1 to 13 which process comprises the following synthetic steps:

i) mono- or dialkylation of an alkynol with glycidol or a glycidol analogue to form a hydrophilic alkyne;
ii) di-iodination or tri-iodination of the double bond(s) in the substituted alkyne from i).

15. A method for the generation of an X-ray contrast image of a human being or an animal, preferably a human being, which method comprises the administration of a contrast agent as claimed in claims 1 to 12, and the generation of an X-ray image.

16. Use of the compounds of claims 8 to 13 as X-ray contrast agents.

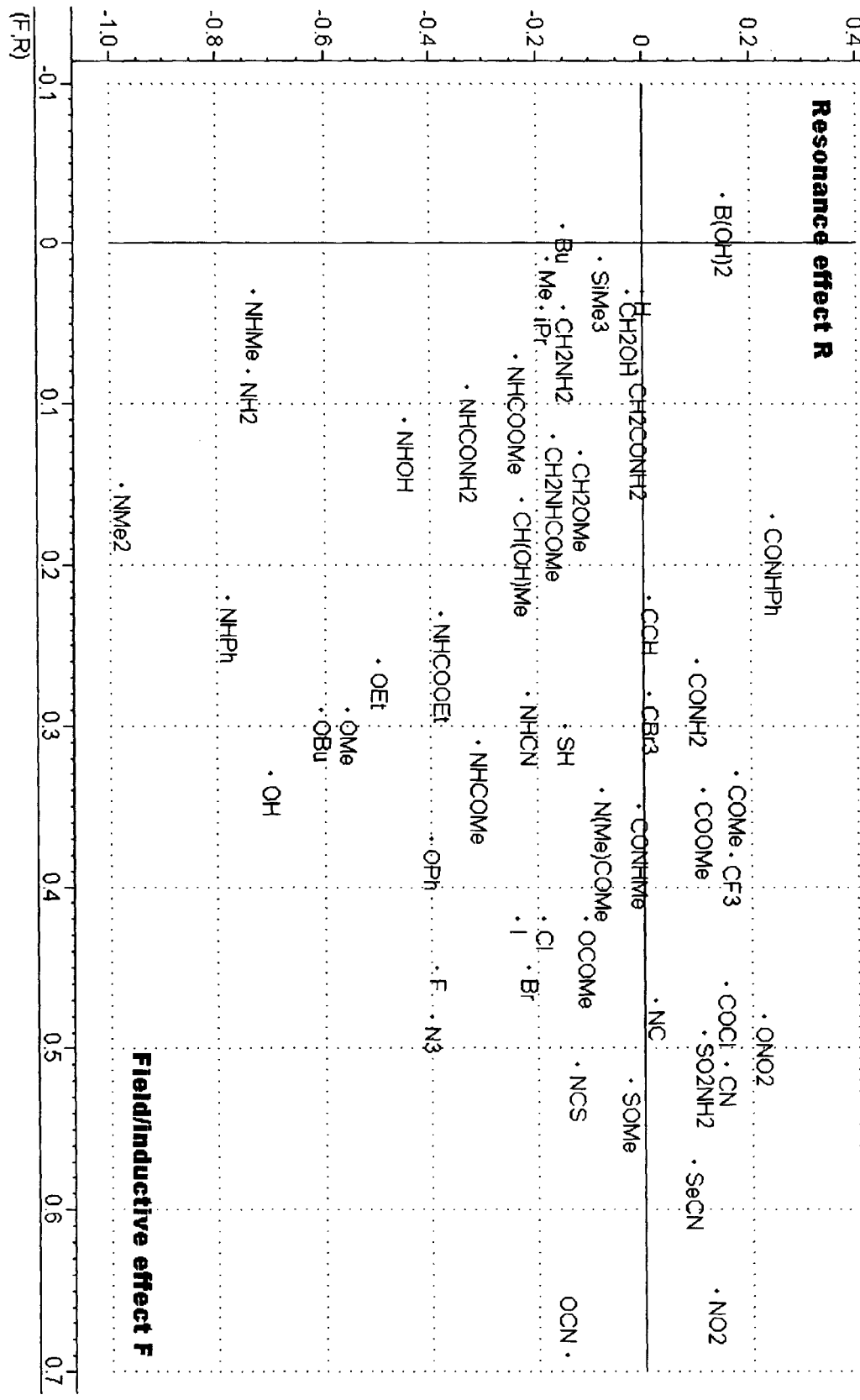


Figure 8: Resonance effect and field/inductive effect for different substituents

Appendix 1